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Compare and contrast: pediatric cancer *versus* adult malignancies

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Abstract
Cancer is a leading cause of death in both adults and children, but in terms of absolute numbers, pediatric cancer is a relatively rare disease. The rarity of pediatric cancer is consistent with our current understanding of how adult malignancies form, emphasizing the view of cancer as a genetic disease caused by the accumulation and selection of unrepaired mutations over time. However, considering those children who develop cancer merely as stochastically "unlucky" does not fully explain the underlying aetiology, which is distinct from that observed in adults. Here, we discuss the differences in cancer genetics, distribution, and microenvironment between adult and pediatric cancers and argue that pediatric tumours need to be seen as a distinct subset with their own distinct therapeutic challenges. While in adults, the benefit of any treatment should outweigh mostly short-term complications, potential long-term effects have a much stronger impact in children. In addition, clinical trials must cope with low participant numbers when evaluating novel treatment strategies, which need to address the specific requirements of children.

Keywords Chronification · Clinical trial design · Chromotrypsis · Driver mutation · Secondary malignancies

1 Introduction and historic perspective

> "A wife who loses a husband is called a widow. A husband who loses a wife is called a widower. A child who loses his parents is called an orphan. There is no word for a parent who loses a child. That's how awful the loss is.", from *An Orphan's Tale* by Jay Neugeboren.

There are currently four independent lines of treatment approaches for cancer: (1) surgical removal, which has probably been performed for more than 3500 years [1]. Even if surgical resection of locally advanced or metastatic tumours, in contrast to tumours diagnosed at an early stage, is often not curative, it remains an important treatment option, as it often significantly expands the therapeutic window [2]. (2) Immunotherapy, which is generally considered to have been initiated by William Coley in the 1890s [3] and, after a long hiatus for technology to catch up, is currently experiencing a renaissance. (3) Radiotherapy–Emile Grubbé first exposed a breast cancer patient to X-rays in 1896 [1]. (4) Chemotherapy–a term that was coined by Paul Ehrlich early in the twentieth century–became relevant in the context of cancer after the Second World War, when decreased levels of leukocytes were detected in soldiers exposed to mustard gas [4]. Based on these observations, Goodman and Gilman treated mice bearing transplanted lymphoid tumours with nitrogen mustard and observed marked regressions [5]. The following year, Sidney Farber treated the first child, 3-year-old Robert Sandler, suffering from acute lymphoblastic leukaemia

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(ALL), with chemotherapy using aminopterin (4-aminopteryol glutamic acid) [6]. Although only a brief response was achieved, it was nevertheless the birth hour of modern, efficient treatment of pediatric cancer. What followed was an unprecedented exchange of knowledge and the build-up of international networks, often held together by the sheer power of personality of those early oncologic pioneers, to ensure the best treatment for their patients. These efforts initiated an incredible success story: in the last 30 years alone, 10-year survival rates for sufferers of childhood leukaemia increased from 27 to 81% [7].

But these successes have also highlighted a new set of problems that distinguish pediatric from adult cancer. Although a leading cause of death for children and adolescents [8], childhood malignancies are actually rare, and the underlying pathogenesis of most pediatric cancers remains largely known. In 2017, 416,500 of 0–14-year-old children suffered from cancer globally [9]. Around 80% of children with cancer who live in high-income countries tend to survive 5 years after diagnosis, compared with ~40% in most low- and middle-income countries [9]. Furthermore, with survivors of childhood cancers now reaching old age, the side effects and long-term health complications now become apparent. So, better access to better drugs specifically geared towards the underage patients is urgently needed, yet the number of anticancer therapies approved for pediatric cancer is significantly smaller compared with adults. According to the US Food and Drug Administration, only 11 drugs have been approved for anticancer therapy in children from 1980 to 2017 [10]. This is partly due to the specific requirements and considerations for a therapy to treat pediatric tumours.

2 Therapeutic endpoints and other considerations

Therapeutic approaches for the treatment of childhood cancers currently mainly differ in one crucial point, namely that, with pediatric patients, long-term considerations of potential treatment side effects are much more pressing. Treatment with DNA-damaging drugs, which make up a large part of chemotherapeutic options [1], or radiation inherently increases the risk of secondary malignancies later in life [11]. Comprehensive studies on this topic are still quite rare, as huge increase in survival of childhood cancer patients occurred only around 40 years ago, i.e. long-term effects are only now becoming apparent and more monitoring/surveillance is needed to form a comprehensive picture [11]. A German study with a follow-up of up to 35 years found secondary malignancies to occur in around 8% of all former patients but does not indicate which percentage is truly associated with side effects of treatment [12].

Other side effects of treating childhood cancer have long been known, such as the cognitive dementia in survivors of childhood medulloblastoma, associated with radiotherapy and first described more than 50 years ago [13]. Variations in application of radio-treatment to pediatric brain tumours and the addition of neuroprotective interventions are currently being investigated and show promise in reducing the long-term side effects. Aside from aforementioned cognitive impairment, there are also endocrinological issues and hearing loss [13]. Of course, similar efforts are being made for other pediatric malignancies as well, like the introduction of a metronomic treatment schedule that avoids the maximal tolerable dose [7].

It should be superfluous to emphasize that despite the side effects the current treatment has, it is the best available option. Historical records, as well as cases where parents refuse treatment, show that no treatment leads to pain and suffering, while even the addition of alternative treatment modalities leads to a significant reduction of patient survival [14].

However, an adaptive, more dynamic treatment schedule, based on inhibition of proliferation and a reduction of tumour-specific features that make the disease invisible to the immune system, and, as we have discussed previously elsewhere, the attempt to chronify the malignancy might be a valuable addition to our therapeutic options [15]. This approach is based on the view of the tumour as an ecological niche where the different clones present in the tumour represent different populations that interact in different ways and support each other, as well as compete for limited resources. To ensure stability of this system, which–when considering cancer–is inherently unstable, one has to consider three key points: (1) avoidance of a drastic change to the ecosystem, comparable to the meteor that wiped out the dinosaurs and allowed for the expansion of the mammalian linages; (2) prevention of the unchecked expansion of the tumour cells which is the underlying cause of the inherent instability and similar to the culling of an apical species without natural enemies; (3) the maintenance of the equilibrium within the ecosystem, i.e. avoid the removal of the dominant subclone or its reduction to such a level that other clones can obtain dominance, or–to put it bluntly–if you kill the fox, you might end up with rabbit troubles in our cabbage patch. It is the latter point which is counterintuitive, as it suggests one should attempt to eradicate the tumour, rather than dynamically manage it to avoid the evolutionary pressure that leads to mutational escape. This mutational escape will lead, *per* definition, to a tumour that is resistant to the current treatment. The alternative dictated by the parameters described above is constantly to manage the tumour so as to keep it localized and at a constant size–a condition a patient might continue to live with.

But what is the evidence that such a chronification approach would work, or indeed, is it even relevant to pediatric cancer? When comparing mutation and amplification or

deletion frequencies in neuroblastoma, a clear difference becomes obvious; while neuroblastoma–like most pediatric tumours–is mainly a disease of amplifications and deletions with an overall low mutational burden, there is an increase of mutations in relapsed neuroblastoma while amplifications/deletions are decreased [16]. This suggests that, upon relapse, typical cancer resistance mechanisms are selected for, ironically making relapsed pediatric cancers as a disease group more similar to adult tumours. Now, the ground-breaking work of Luria and Delbrück [17], as well as many other independent lines of evidence, for example, the presence of bacterial populations in 30,000-year-old permafrost resistant to modern antibiotics [18], suggests that resistance mechanisms are often already present, but as discussed above, modern treatment options are mutagenic in themselves, so might even enhance this emergence.

Gatenby and co-workers experimentally showed that an adaptive strategy reduces tumour burden for a prolonged time when compared with a rigid protocol [19] and our own clinical experience with the RIST protocol, a complex combination therapy applied in a compassionate use setting, suggests that chronification is possible [20]. Technical and monetary limitations aside, i.e. the need for regular monitoring of tumour progression, the key question which needs to be answered is when to apply conventional therapy, which–after all–can, with certain pediatric cancers, achieve a 10-year survival rate of almost 100% [7]. Other tumours, like the rare pediatric glioblastoma, remain virtually incurable with current treatment approaches [21], i.e. here an attempt to chronify the disease might lead to an increase in quality and quantity of the patient's life. While the extremes on the spectrum of pediatric cancers which most benefit from conventional therapy or adaptive approaches are easily made out, for the majority of cancers and subgroups, such data is not readily available. More information is needed, for subtyping and designing predictive models if and when and what resistance mechanisms might arise, as well as evaluation ad to whether childhood development, particularly puberty, might lead to extreme changes the in cancer microenvironment that suffice to destroy the necessary stability underlying chronifying treatment. This can only be achieved by large-scale clinical evaluations.

3 Evaluating novel treatment strategies

As already mentioned, while cancer is among the leading causes of death among children and adolescents, in terms of total numbers, it is still a relatively rare event. This, in turn, makes optimizing therapeutic intervention, specifically geared at children, rather difficult as traditional clinical trial designs rely on large participant numbers. When recently surveying trials registered with the US-American government (clinicaltrials.gov) which is increasingly becoming a prerequisite for publishing results in the peer-reviewed literature, we found that the total number of clinical trials specifically for children (0–14 years) or children and adolescents (0–21 years) has continuously increased over the last quarter century. Nevertheless, those still only account respectively for 0.33% and 2.18% of all clinical trials pertaining to cancer from 2012 to 2017 [7]. Even when also considering studies that are open to mixed or all age groups, they only make up 6.55% of all relevant studies [7]. Mathematically, this actually still means that pediatric cancer, which makes up about 0.22% of all cancer incidences, is–in terms of studies per incidences–overrepresented [7].

The great therapeutic advances that turned around the 10-year survival expectancies for pediatric leukaemia from 27 to 81% in a period of 30 years [7] were due to the cooperation of many clinics and study groups which facilitated the free exchange of patient histories and treatment protocols and allowed for a systematic analysis of treatment outcomes [22]. After the initial success, foremost for ALL in the 1970s, similar approaches were implemented for almost all pediatric tumours, often setting a European standard and thus allowing for international cooperation. Consequently, sufficient numbers of participants were included in clinical trials which allowed the evaluation of rarer malignancies [22].

However, concerning treatment approaches specifically geared towards children, clinical trials, of course, remain the gold standard. Here, new designs have also been implemented to lower the number of participants needed for a statistical evaluation and to shorten the time a potential new treatment approach needs from evaluation to clinical implementation. In their comprehensive review of innovations for pediatric oncology trials, Doussau, Geoerger, Jiménez, and Paoletti identify three key areas of innovation [23]: (1) relaxing the rules for more flexible inclusions, (2) incorporating data emerging from adult studies, (3) accounting for toxicity evaluation at repeated cycles. Probably the most widely known innovation regarding the organization of pediatric oncology trials is the introduction of the rolling 6 design, which was predicted by computer simulation in 2008 to shorten significantly the phase I duration without increasing the risk of toxicity [24]. In 2014, more than 40% of all pediatric phase I oncology trials used this design [23]. The traditional 3 + 3 design, which is based on the up and down method introduced by Dixon and Mood in 1948, relies on the assumption that the dose recommended for phase II studies should induce dose-limiting toxicities in less than 33.3% of all patients. There are several other rule-based or model-based designs, as well as designs for specialized conditions such as combination therapy and to investigate molecular targeted agents [25], but low absolute numbers of patients remains a huge problem. Fletcher and colleagues recently proposed a multi-arm multi-stage or adaptive trial for newly diagnosed, high-risk neuroblastoma patients [16]. Here, patients are initially treated, when possible, based on the

molecular profile of their tumour or, in the absence of clear indicators, are randomized into one of the parallel running arms of the trial. Through continuous monitoring, patients can be moved to experimental treatment if their tumours do not respond favourably to the initial treatment [16]. The two major problems of treatment options for pediatric oncology patients are further highlighted by Fletcher's choice of title, despite neuroblastoma being the most common extracranial solid tumour in childhood, accounting for 8–10% of all childhood malignancies [26]: the review is called *Too many targets, not enough patients: rethinking neuroblastoma clinical trials* [16]. The second problem, also alluded to in the title, is the distinct lack of targetable mutations in pediatric tumours. Does this in turn mean that pediatric and adult tumours should be viewed as distinct classes of disease?

4 Are pediatric cancer and adult malignancies two different classes of disease?

Cancer is considered to be an accumulation of mutations over time. In a set of studies, Tomasetti and Vogelstein showed that there is a strict correlation between the estimated number of (stem) cells within a given tissue and the number of lifetime cell divisions and, thus, the risk of developing cancer, if one ignores cancers that have a clear and well-defined aetiology, such as smoking-induced lung cancer [27, 28]. While these studies are not without controversy (for example, [29–32], the main conclusion that approximately 66% of cancer-causing mutations arise without an overt external reason is supported by independent data that suggest that 38% of all cancers are actually preventable, with smoking still being the largest identifiable cause of cancer [33]. The notion of cancer as an accumulation of mutations over time is further supported by the fact that more than half of all malignancies occur in individuals older than 70 years of age [34]. However, despite an overlap in underlying molecular mechanisms regulating both ageing and cancer [35], such as genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, and other mechanisms [36, 37], one should not reduce cancer merely to a consequence of ageing. The cumulative risk for developing cancer only increases to the age of 70 years and then begins to decline again; cancer is actually a rare cause of death after the age of 90 [35].

While initial mathematical models that were designed more than 60 years ago suggested that a series of six or seven mutations in oncogenes and tumour suppressor genes is required to develop a malignant tumour from normal cells [38], more recent studies on lung and colon adenocarcinomas have shown that as little as three sequential mutations can lead to a malignant phenotype [39]. These mutations can theoretically occur in a single cell but in practical terms will most likely accumulate in the prodigy of the cell hit with the initial mutation. This progression is reflected in several key features of adult cancers, for example most carcinomas undergo a clear progression from hyperplasia, dysplasia, *in situ* tumour to invasive tumour [40], or similarly that the invasion-metastasis cascade can be described as a gradual acquisition of additional features necessary for the transition of a stationary cell located in a well-defined surrounding to a highly mobile cell, which is capable of surviving in a hostile environment [41].

Now, if we take this setup and apply it to pediatric cancer and go by the default assumption of *ceteris paribus*, we need to postulate that children who develop cancer have just been stochastically "unlucky" and the three to seven mutations accumulated by sheer chance more rapidly in an individual cell and its offspring than is the average. While this observation fits the fact that childhood cancer is a very rare event, it fails to explain other observations. For those cancers which are not overtly associated with risky behaviour, such as smoking, alcohol consumption etc., i.e. for the 66% of all cancer-causing mutations, one would expect similar tumours to develop at similar tissue locations in children and adults, which is not the case [7]. Probably, the most obvious difference can be found in leukaemia. Even, when ignoring the differences in subtypes, leukaemias make up one-third of all pediatric malignancies [42] and are the most common cancers in children, but only the 12th most common cancers when looking at all age groups [43]. Neuroblastoma is the most common extracranial solid tumour in childhood [26], but virtually unknown in adults [44]. But we also see this difference between adults and children within an individual tissue; medulloblastoma is the most common pediatric malignant brain tumour, but rare in adults, while with glioblastoma, it is exactly the opposite [45]. Are these differences explained by different aetiologies of pediatric and adult cancers or are they due to the tissue of tumour origin changing during ontogeny. Why the latter aspect can serve as explanation for differences in certain tumours, such as breast cancer, where factors like early puberty and late menopause [46–49] are known to enhance cancer development, so that one would–intuitively–expect less breast cancer incidences in children, it does not explain other differences.

In addition, several data points suggest that the majority of mutations accumulate during ontogeny and the most significant telomere shortening occurs before birth [50]. This would suggest that the majority of relevant genetic alterations should have occurred prior to the end of puberty. Following this line of argument would suggest that pediatric cancer is an accumulation of mutations over time and as such a relatively rarer event, while additional factors, suggested by DeGregori to be "age-dependent alteration of selection for oncogenic mutations" cause the observed age-dependent increase in adult cancer [50]. Yet, congenital cancer is incredibly rare, accounting for only 1–2% of pediatric cancers [51] and it remains unclear why. In those malignancies that have a clear driver

mutation, data suggest that this mutation occurred prenatally, while the disease only emerged later during infancy, as is the case, for example in B cell ALL [52].

In addition, it has been proposed that cancer can also occur after a single catastrophic event that leads to complex chromosomal rearrangements, termed chromothripsis. While there is little doubt that these rearrangements can occur, these chromosomal alterations do not contradict a cumulative progressive origin of the tumour [53]. Indeed, a single catastrophic event has never been observed, so that it is conceivable that chromosome breakages might occur during several rounds of cell cycle progression [54]. So, is chromothripsis a major contributor to the development of pediatric cancers? Koltsova and co-workers performed a comprehensive review of evidence for chromotrypsis, or large chromosomal rearrangements, in several cancers and identified several incidences in pediatric cancer [55]. Thirteen percent of medulloblastoma show evidence of chromotrypsis, with 100% of tumours belonging to the Sonic-Hedgehog (SHH) subgroup with mutant TP53 gene and 0% of the SHH subgroup with wildtype TP53 [56]. Indeed, there seems to be a link between mutant TP53 and chromotrypsis, as the incidence rate in acute myeloid leukaemia (AML) is also elevated from 1 to 47% if TP53 is found to be mutated [56]. In another leukaemia, ALL with intrachromosomal amplification of chromosome 21 (iAMP21), 89% of investigated cases showed evidence of chromotrypsis [57], but this is an incredibly rare leukaemia, accounting for only 2.4% of all pediatric B cell ALL [58]. In addition, 18% of high-stage neuroblastomas were associated with this event [59]. With exception of the data for the rare ALL with iAMP21, these numbers are not unusually high when compared with adult malignancies. For example, 60% of invasive bladder carcinoma show signs of chromotrypsis [60], while any other tumours are found in the 30–40% range [55]. The aforementioned study investigating the genomic alterations in pediatric cancers again found an association between chromotrypsis and TP53 mutations, but does not highlight the particular genetic alteration as strongly associated with childhood malignancies [61].

Germline mutations have also been suggested to contribute to the development of pediatric cancer, however. Although there are some predisposing genetic factors that increase the risk of childhood malignancies, they do not appear as common (or remain largely unidentified, which would suggest a low penetrance) as to explain the clinical reality. The best-known example of this is germline mutations in one allele of retinoblastoma protein (RB1), which, together with somatic inactivation of the second allele, give rise to retinoblastoma [62]. More than 90% of retinoblastoma cases are diagnosed before 5 years of age, but less than 25% of retinoblastoma cases are bilateral, normally indicative of the presence germline mutations [63]. The presence of a germline mutation in RB1 also predisposes to additional malignancies, especially sarcomas and melanoma [63]. Another well-studied example of predisposition is the autosomal dominant Li-Fraumeni syndrome, caused by heterozygous germline mutations in the tumour suppressor TP53 gene. It is characterized by the development of rare tumours in childhood and early onset of cancer in adulthood [64]. It has also been reported that shorter telomeres and, as already discussed, chromothripsis are observed in the presence of TP53 mutations, which might be relevant in childhood cancer [56, 65, 66].

Other studies on the causal mechanism of childhood cancer have demonstrated that children with Fanconi anaemia are more prone to develop cancer at a median age of 16 years [67]. In Fanconi anaemia, BRCA2 mutations along with 15 other potential mutations have been reported [68], leading to congenital abnormalities, bone marrow failure, and a higher risk of developing myeloid and solid malignancies [67, 69]. In addition, pleuropulmonary blastoma, which is associated with germline DICER1 mutations [70], mostly occurs in infants and young children and can give rise to pediatric lung cancers [71, 72]. Trisomy 21, Down syndrome, greatly increases the risk of leukaemia and germ cell tumours [73]. It has been estimated that affected children have a 500-fold higher risk of developing acute leukaemia compared with the general population [74]. Other hereditary cancer predisposition syndromes that are associated with increased risk of pediatric cancer include constitutional mismatch repair deficiency, familial adenomatous polyposis, familial neuroblastoma, xeroderma pigmentosum, hereditary paraganglioma-pheochromocytoma, juvenile polyposis syndrome, multiple endocrine neoplasia type 1 and 2, neurofibromatosis type 1 and 2, Peutz-Jeghers syndrome, phosphatase and tensin homologue hamartoma tumour syndrome, rhabdoid tumour predisposition syndrome 1, and von Hippel-Lindau syndrome [75]. It is interesting to point out that older maternal age increases the risk for most common childhood cancer by 6–15% [76]. This is at first counterintuitive, as mutations leading to heritable retinoblastoma are predominantly from the paternal germline for instance [77]. It has also been suggested that mutations occur less frequently in oocytes compared with sperm due to the fact that oocytes undergo fewer cell divisions during gametogenesis [78]. Nevertheless, it is more probable that ageing affects the maternal germline due to DNA damage response, differential expression of genes in cell cycle control, and repair pathways [79–81].

However, when looking at the sum total heredity cancers account for only 5–10% of all childhood cancer [82] and up to 10% of all cancers in adults [83], i.e. their contribution to all cancers, although higher than predicted a few years ago, is roughly equal in adults and children.

There are, of course, also additional environmental risk factors which have been identified as contributing to the risk of cancer in children. However, in order to measure the influence of environmental exposures on childhood cancer,

prospective studies need to be done, which require millions of children to generate statistically meaningful results. Therefore, most of these epidemiological studies rely on a case-control design. Nevertheless, the true magnitude of effects is difficult to quantify, as is the identification of a causal relationship.

Ionizing radiation is, or at least was, undoubtedly the single most important environmental contributor to childhood cancer. Half a century ago, as many as 1 in 20 cases of childhood cancer may have been attributed to obstetric X-rays, which nowadays are supplanted by ultrasound [84]. A large national study of cancer following computed tomography scans before the age of 22 years reported that a cumulative dose of 50 mGy might triple the risk of leukaemia, while 60 mGy might triple the risk of central nervous system (CNS) tumour [85]. While, as already discussed, exposure to radiotherapy and chemotherapy can be carcinogenic themselves, the resulting secondary malignancies only develop later in life, i.e. are associated with adulthood and not late childhood [86]. It has also been estimated that approximately 15% of childhood leukaemia in Britain might be due to natural background ionizing radiation [87]. Moreover, it has been observed that children with xeroderma pigmentosum are highly susceptible to ultraviolet exposure and they are more likely to develop skin cancer during their childhood [88].

Other studies looking into environmental risk factors reported mostly null or slightly elevated risk of pediatric cancer in association with exposure to maternal coffee [89], vitamin use [90], and both parental and maternal smoking [91, 92], but found that maternal alcohol consumption during pregnancy notably increases the risk of childhood AML [93]. Other factors that have been identified as contributors to childhood cancer include high birth weight, notably leukaemia [94, 95], CNS tumours [96], and neuroblastoma [97], very low birth weight which greatly increases the risk of hepatoblastoma [98] and having a twin [99, 100].

So far, no major risk factors have been identified to explain fully the occurrence and the distribution patterns of childhood cancers, yet the null hypothesis that those children just suffer from extra bad luck seems inappropriate fully to explain the given epidemiology. Therefore, looking into the (most likely multifactorial) causes and the specificities of pediatric cancers remains an important, central tenet of oncological research.

5 Conclusions and outlook

When comparing pediatric malignancies with adult, it is important to find both common ground to implement new successful treatment strategies quickly and emphasize the differences, so as more effectively to gear treatment to the specific group of oncological diseases.

A key point to remember is the urgent need for novel therapies, which is illustrated by the high number of pediatric cancer–related deaths, although already effectively reduced since the 1970s, and the grave sequelae suffered by the survivors, such as the development of secondary malignancies [7, 22, 101]. A potential approach is the use of precision or personalized medicine, targeting mutationally deregulated pathways to induce apoptosis. This approach is, of course, of interest to both adult and pediatric medicine; however, pediatric oncology faces additional obstacles. First is the lack of identifiable targets. As we discussed, pediatric tumours are more likely to be diseases of upregulation or downregulation of protein expression and, therefore, express only a reduced number of tumour-specific targets, i.e. proteins that, due to mutations, express a uniquely targetable sequence. A recent analysis suggests that slightly over half of all pediatric patients express an identifiable, druggable target [61].

This is often referred to as the problem of the driverless car: if you have no driver (mutation) to target, how do you stop the car? The answer is by targeting the engine, which is unfortunately not different from all the engines powering non-cancerous cells. In addition, one must bear in mind the intratumoural heterogeneity, leading to the emergence of a treatment-resistant subclone by upregulating a partially inhibited or activating an alternative pathway [7, 102]. To prevent this, one might combine already available kinase inhibitors, cell death–inducing ligands and BH3 mimetics, targeting the tumour from different angles. Additionally, this combination therapy should include immunotherapy to make use of the patient's innate and adaptive immune system. To circumvent the central obstacle of cancer immunotherapy, the immune evasion by the loss of targeted antigens, we suggest the implementation of T cell receptor-based therapy targeting the tumoral microenvironment, such as proteins essential for tumour cell survival [7, 103]. We envision a strategy combining several drugs with mild effects on individual pathways, so as to minimize side effects in healthy tissues and not deplete the immune system that synergistically depletes the energy of the tumour cells. In addition to finding the right combination partners, bearing in mind that the most potent single agents are not necessarily the best combination partners, delivery and sequence of drug application will be major points to consider. One of the key differences between adult and pediatric tumours is the relative lack of targetable alterations in pediatric cancers. Pediatric tumours are not dominant diseases of mutations [61]. Indeed, in around 10% of all pediatric tumours, no mutation can be identified at all [51]. But maybe one should consider it as a boon and not merely as the cause for the absence of druggable targets? If pediatric cancers should predominantly be viewed as diseases of epigenetics [51], this, in turn, also suggests a genetically more stable target that can be addressed with drugs that alter reversible DNA modifications.

When personalized medicine is discussed, it is most frequently in the context of chemotherapy, but it is worth bearing in mind that this is not a novel concept *per se*. In the context of surgical removal, it has long been standard to treat each tumour as an individual case when planning the maximal removal while causing minimal damage to the surrounding tissue. Here too, pediatric tumours represent their own unique challenges, dealing with smaller organs and more devastating long-term consequences. It is also a skill more difficult to teach and develop than a data-based personalized drug treatment, and while novel approaches, such as the da Vinci surgical system or the Brain Suite, might facilitate increased three-dimensional planning and precision surgery, very little beats experience and good mentoring.

To address several of the issues raised, one has to implement more first-in-child clinical trials to evaluate efficiently such combination therapies while maintaining a good safety-profile [101]. Due to the low numbers of total pediatric cancer cases, more flexible trial designs and more international cooperation are absolutely essential.

From the researcher's perspective, the aetiology and the kinetics of pediatric cancers still leave many open questions. In particular questions regarding the necessary, but insufficient genetic background that permits the emergence of pediatric cancer growth, and identifying the driving conditions underlying these malignancies remain key issues to be addressed. *Per* definition, the microenvironment in which a tumour thrives is different in children and adults, after all "[p]ediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies…", but we do not know the variation within the childhood population. For example, it is tempting to speculate that children developing cancer might be represented by a group that has less efficient DNA repair, or genomic stability, or cells that deal less efficiently with oxygen radicals, maybe even only in a tissue-specific fashion, than the average child. While the treatment of pediatric cancers has been a success story in terms of quality and quantity of convalescent's life, this should merely serve as a reminder of what we owe to those that went before us and, most importantly, what we owe to our little patients and their families, or, to finish the quote above "…[pediatric] has its own independent range and horizon and gives as much to general medicine as it receives from it" [104].

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